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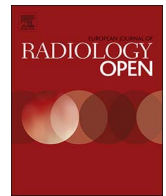


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## Case report

## Hepatic adenomatosis in liver cirrhosis

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## ABSTRACT

Hepatocellular adenoma (HCA) is a benign liver tumor most frequently occurring in women using oral contraception. HCA develops in normal or nearly normal livers and is extremely rare in cirrhosis. The authors present magnetic resonance imaging and histopathologic findings in a 57-year-old man with liver cirrhosis and hepatic adenomatosis.

As the differentiation between HCA and hepatocellular carcinoma (HCC) can be difficult with imaging, we would like to highlight the importance of ancillary findings such as the presence of iron on MRI, which can be observed in HCA.

## 1. Introduction

Hepatocellular adenoma (HCA) is a benign liver tumor most frequently occurring in women using oral contraception. HCA develops in normal or nearly normal livers and is extremely rare in cirrhosis. Here, we report a case of a patient who has undergone abdominal magnetic resonance imaging (MRI) with the incidental finding of hepatic adenomatosis (HA) in the setting of liver cirrhosis.

## 1.1. Case

A 57-year-old man with abdominal pain was referred to our hospital. His medical history included alcohol abuse, tobacco use and elevated BMI (27.4 kg/m<sup>2</sup>). He had no history of diabetes or anabolic steroid use. The physical exam revealed no stigmata of advanced liver disease.

Laboratory tests showed elevated gamma-glutamyltransferase (1466 U/l) and alkaline phosphatase (211 U/l); aspartate transaminase, alanine transaminase, international normalized ratio, albumin, bilirubin, and alpha-fetoprotein were normal. Viral hepatitis serologies were negative.

MRI of the abdomen revealed a liver with nodular surface compatible with cirrhosis. There were multiple (> 10) non-fat containing liver lesions measuring up to 5 cm, appearing hyper- or isointense on pre-

contrast fat suppressed T1-weighted imaging (T1WI), mildly hyper-, iso- or hypointense on fat suppressed T2WI with intense enhancement on T1WI obtained during the arterial phase after injection of a gadolinium-based contrast agent (gadopentetate dimeglumine, Magnevist, Bayer Healthcare) with washout on portal venous phase and a pseudocapsule. Some of these lesions showed signal intensity drop on in-phase compared to out-of-phase images, indicating iron content (Fig. 1). No vascular invasion was identified. There were no signs of portal hypertension. The lesions were interpreted as multifocal HCC. After an inconclusive fine needle aspiration, a laparoscopic surgical resection of two lesions revealed HCAs with positive serum amyloid A (SAA) and C-reactive protein (CRP) on immunohistochemical stains (Fig. 2). The  $\beta$ -catenin stain was negative. There was background liver cirrhosis, presumed to be due to alcohol abuse. Follow-up computed tomography (CT) 6 months later showed stable remaining lesions.

## 2. Discussion

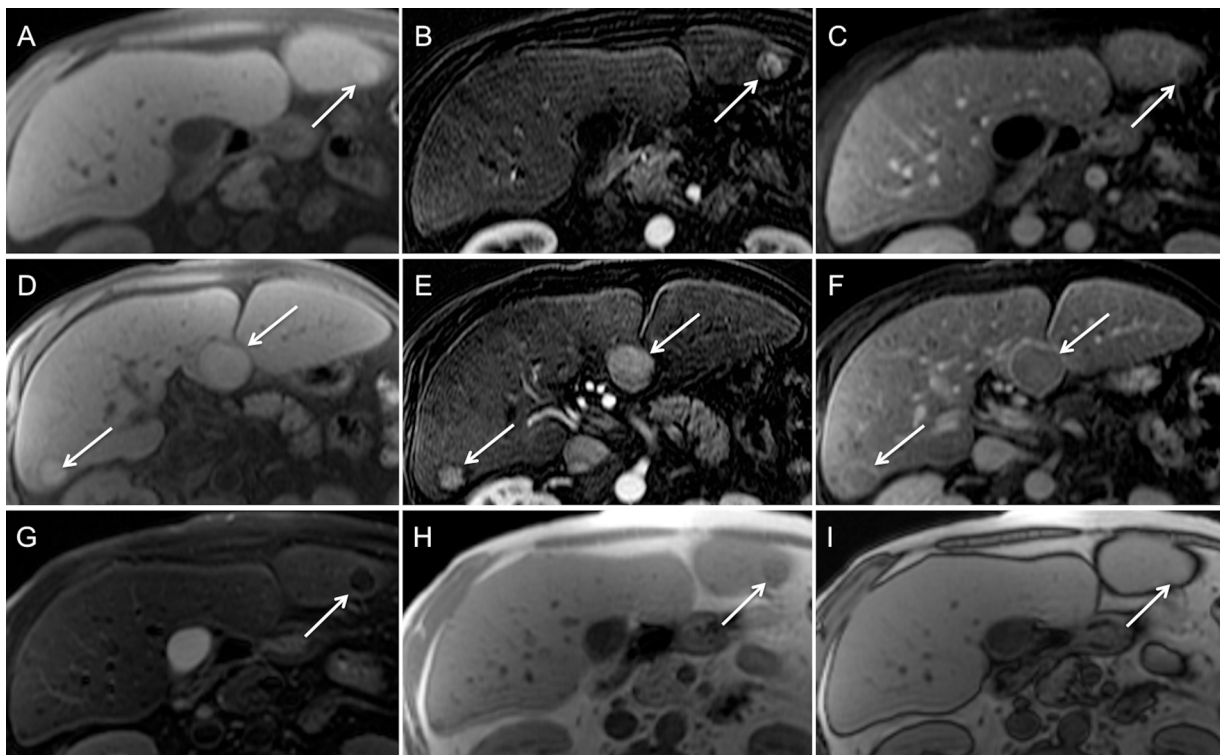
HCA develops in normal or nearly normal livers and is extremely rare in cirrhosis. The predisposing factors for developing HCA include excessive hormonal or metabolic exposures, such as oral contraceptives, anabolic steroids, glycogen storage disease, and type 2 diabetes. Case-reports of HCA have been reported in cardiac cirrhosis [1] and in fibrosis without known risk factors of HCA [2], all in male patients, as in

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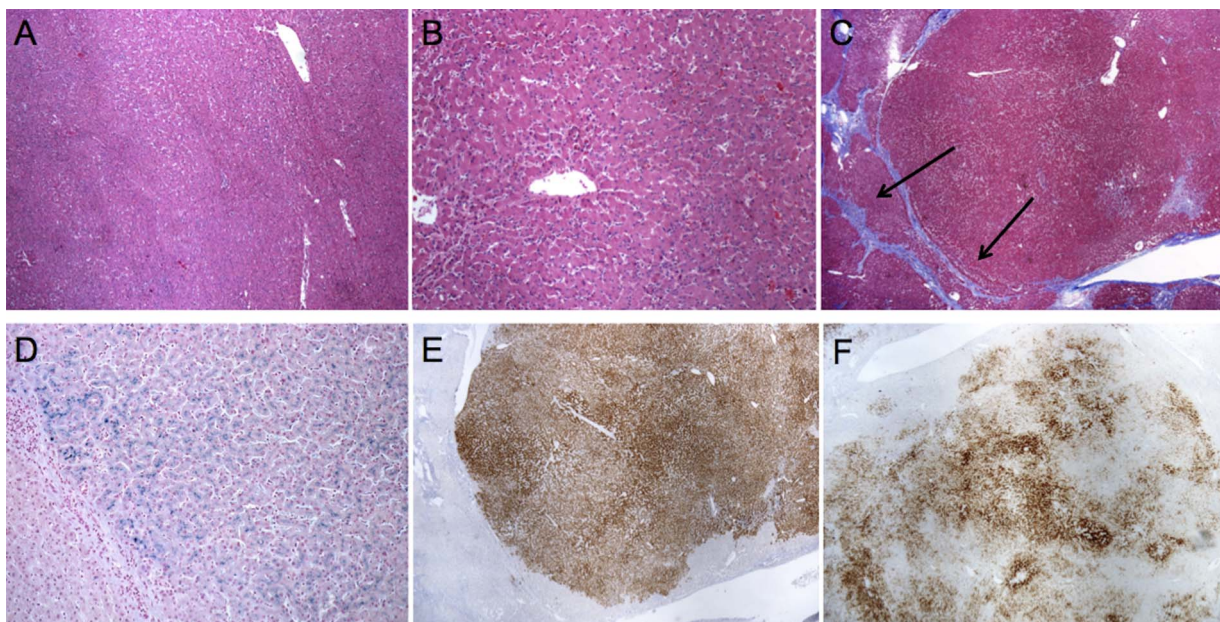


**Fig. 1.** Contrast-enhanced magnetic resonance imaging in a 57-year-old patient with alcoholic cirrhosis shows multiple mildly T1 hyperintense lesions in the right and left hepatic lobes (arrows) on pre-contrast T1-weighted images (A, D at different levels) with enhancement on subtracted arterial phase images (B, E) and washout on the subtracted portal venous phase images with pseudo-capsule enhancement (C, F). The lesion in segment III (seen on A, B, C, G, H, I) is hypointense on T2-weighted fat suppressed image (G) and shows signal drop on in-phase (H) compared to out-of-phase images (D), indicating iron content. The lesion in segment III was resected. Note liver surface nodularity compatible with cirrhosis.

our case.

Whereby HCA may contain iron, it is very unusual for HCC [3]. HCA may lack portal venous inflow and thus can be hypervascular on arterial phase on CT or MRI. It is often difficult to differentiate between HCA and HCC on imaging, due to overlapping appearances, and HCC is the main diagnosis to consider in cirrhosis.

Liver specific gadolinium based contrast agents [such as gadobenate disodium (Gd-BOPTA, Multihance®) and gadoxetate disodium (Gd-EOB-DTPA, Primovist or Eovist®)] facilitate the differentiation of HCA from FNH [4]. While the majority of FNHs shows an equal or stronger OATP1B3 expression relative to the surrounding liver with an iso-/hyperintensity in the hepatobiliary phase of gadoxetic acid-enhanced



**Fig. 2.** Histopathologic images of resected hepatocellular adenoma show: (A) on H & E stain (x40), monotonous hepatocytes without atypia, and absence of portal tracts. (B) on H & E stain (x100) the hepatocytes are arranged in two cell-thick plates. (C) on Trichrome stain (x20), cirrhotic nodules encircled by fibrous septa (arrows), (D) on Perl stain (x100) coarse iron granules in the adenoma, but not in the surrounding liver. The adenoma is diffusely and strongly positive for CRP (immunostain, x20) (E) with patchy serum amyloid A reactivity (immunostain, x20) (F).



MRI [5,6], most HCAs have a decreased expression of OATP1B3 resulting in an hypointense signal on delayed hepatobiliary phase images [7,8]. Diffusion-weighted (DW) MRI can be used for liver lesion characterization, with better results compared with T2-weighted imaging [9–12] and with potential additional value to contrast-enhanced sequences. HCAs, however, have intermediate ADC values that can overlap with those of malignant lesions and normal liver parenchyma [13–16]. As DW MRI is a marker of cellularity HCAs may sometimes display restricted diffusion. On the other hand, necrotic malignant lesions can demonstrate high ADC values.

Using molecular markers and immunohistochemistry, HCAs can be classified in eight main subtypes: hepatocyte nuclear factor-1 $\alpha$  (HNF1 $\alpha$ )-mutated, SAA/CRP-positive inflammatory HCA (IHCA),  $\beta$ -catenin exon 7/8,  $\beta$ -catenin exon 3, mixed b<sup>ex7,8</sup> IHCA, mixed b<sup>ex3</sup> IHCA, sonic hedgehog and unclassified [17]. HCAs in men were shown to be usually SAA/CRP-positive, occur singly, and arise from factors also found in development of HCC in non-cirrhotic liver such as alcohol use, tobacco use and elevated BMI [18]. Our patient was SAA/CRP-positive, similar to a prior report [2] and had HA. However, SAA or CRP expression is not specific for IHCA, these proteins are known to be produced by hepatocytes and may be overexpressed in cirrhotic nodules under local or systemic inflammatory conditions [19].

The estimated risk for malignant transformation of HCA is between 4% and 8% [20]. All subtypes of HCA may demonstrate borderline features of typical foci of HCC. However, the  $\beta$ -catenin mutated HCA and mixed b<sup>ex3</sup> IHCA subgroups are the most prone to malignant transformation [21–23].

During hepatocarcinogenesis, iron may accumulate in low-grade dysplastic nodules (DNs) and in some high-grade DN. These nodules containing an iron deposit are referred to as ‘siderotic nodules’. In hepatocytes of siderotic nodules, the iron transporter system, such as the transferrin transporter, are upregulated [24]. However, as these nodules progress into HCCs, the iron-transportation system also alters, and iron utilization increases, thus causing iron deficiency in HCCs [25]. However, HCAs may deposit iron [26–28] and Cheng et al. [27] even proposed the term siderotic hepatic adenoma in these cases.

### 3. Conclusion

Our case supports the existence of HCA/HA in the setting of cirrhosis. As the differentiation between HCA and HCC is often difficult with imaging, it is advisable to perform a short-term follow-up imaging and/or tissue sampling for a definitive diagnosis.

### Conflicts of interest

The authors declare that they have no conflict of interest.

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